NTP
National Toxicology Program

Hydroxyurea Research Concept

Barry McIntyre, Ph.D., DABT
National Institute of Environmental Health Sciences

NTP Board of Scientific Counselors
June 22, 2010

Background on NTP's Interest in Hydroxyurea

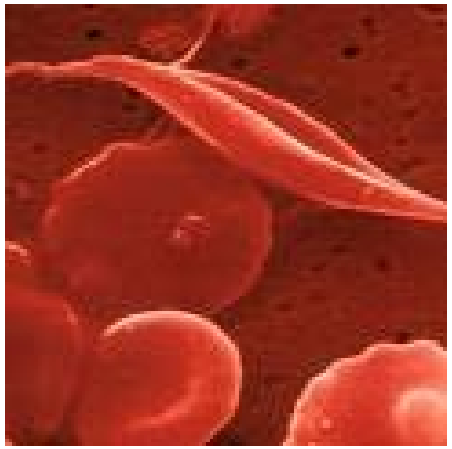
- Off-patent pharmaceutical
  - Originally developed for cancer indications; now also labeled for treatment of sickle cell anemia in adults
- Reviewed by expert panel convened by the NTP Center for the Evaluation of Risks to Human Reproduction (CERHR) (2007)
  - Recommended multi-generation experimental animal studies to assess the long-term effects of prenatal and postnatal exposures on postnatal development including developmental neurotoxicity, reproductive function, and carcinogenicity
- Nominated to the NTP for toxicological testing by a private citizen (2006) and the NIEHS (based on the CERHR report)
  - Wide clinical use in the treatment of rare, but serious diseases
  - Demonstrated mutagenicity and clastogenicity
    - Lack of robust carcinogenicity and reproductive studies and concern regarding safety associated with long-term use
      - Including long-term effects on immunological and neurological development
  - Increasing use in infants/children (and during pregnancy)

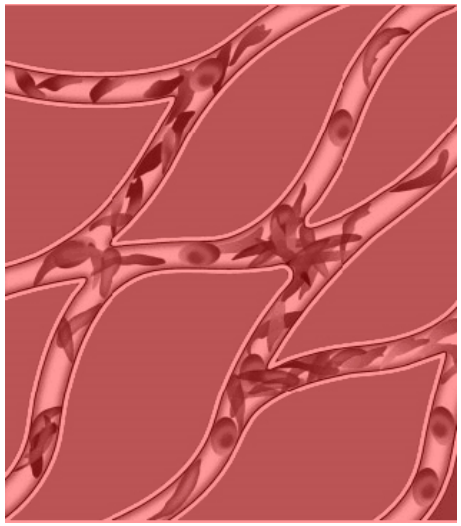
Background (continued)

- Initial nomination was reviewed by the NTP Board of Scientific Counselors in November 2008, and the NTP recommended (and the BSC concurred) that no additional work should be done at that time.
- NIH Consensus Development Conference on Sickle Cell Disease indicated that additional studies in animals would be beneficial to characterize adverse developmental and reproductive effects and carcinogenic risks of hydroxyurea.
- Sponsor (BMS) was asked to conduct a pediatric studies, but they declined
- Clinical trials in infants and children are being conducted, and are showing efficacy.
- Conduct of additional animals studies is supported
  - NTP Interagency review committee
  - National Institute of Child Health and Human Development

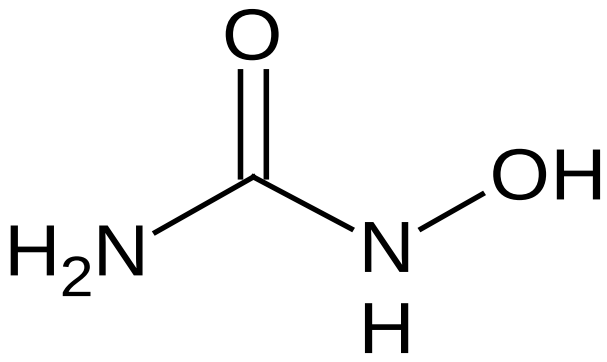
Sickle Cell Disease

- Group of genetic disorders (hemoglobinopathies)
  - Affects 1 in 5,000 Americans (~72,000)
  - Affects primarily individuals of African descent (1 in 500 live births)
- Most severe form is sickle cell anemia
  - Homozygous for Hb S mutation
  - Single A →T mutation in β-globin gene (Gln → Val)
  - Hb S polymerizes in red blood cells (RBC) under low oxygen tension
  - Loss of RBC flexibility and “sickling” → obstructed blood flow
    - “Vaso-occlusive crises”
  - Heterozygosity provides survival advantage to malarial infection





Hydroxyurea



- Only approved disease-modifying therapy for sickle cell anemia
- Inhibits ribonucleotide reductase
  - Inhibition of DNA synthesis → S-phase cytotoxicity → ultimately increased production of hemoglobin F (HBF)
  - Hb F does not have β-globin chains (has γ) and inhibits polymerization of Hb S
- Decreases incidence and severity of vaso-occlusive crises

Hydroxyurea: Clinical Use

- Branded and generic hydroxyurea products
- Approved to treat sickle cell disease (1998) and certain cancers (1967) in adults
- Off-label use to treat:
  - Sickle cell disease in children
  - Myeloproliferative disorders
  - Thalassemia
  - HIV infection
- Active clinical studies evaluating hydroxyurea as a sickle cell therapy in children (including infants)
- Not recommended for use during pregnancy (black box warning)
  - Is used to mitigate the severity of vaso-occlusive crises in pregnant women
- Long-term therapy (lifetime)

Hydroxyurea: Carcinogenic Potential

- Unequivocal genotoxicant
- Case reports of acute leukemia and skin cancers
- Increased incidence of acute leukemia and myelodysplastic syndrome in small cohort studies
- Increased incidence of mammary tumors in female rats (not conducted by the Sponsor).
  - Non-standard design (6-month exposure paradigm; IP, two dose levels, 3X weekly).
- Twelve-month mouse study exhibited no evidence of carcinogenesis (not conducted by the Sponsor)
  - One dose level; IP dosing weekly
- Inadequate evidence for carcinogenicity in humans or experimental animals
  - International Agency for Research on Cancer (2000): Group 3 “not classifiable as to its carcinogenicity to humans”

International Conference on Harmonisation (ICH) GUIDELINE ON THE NEED FOR CARCINOGENICITY STUDIES OF PHARMACEUTICALS S1A

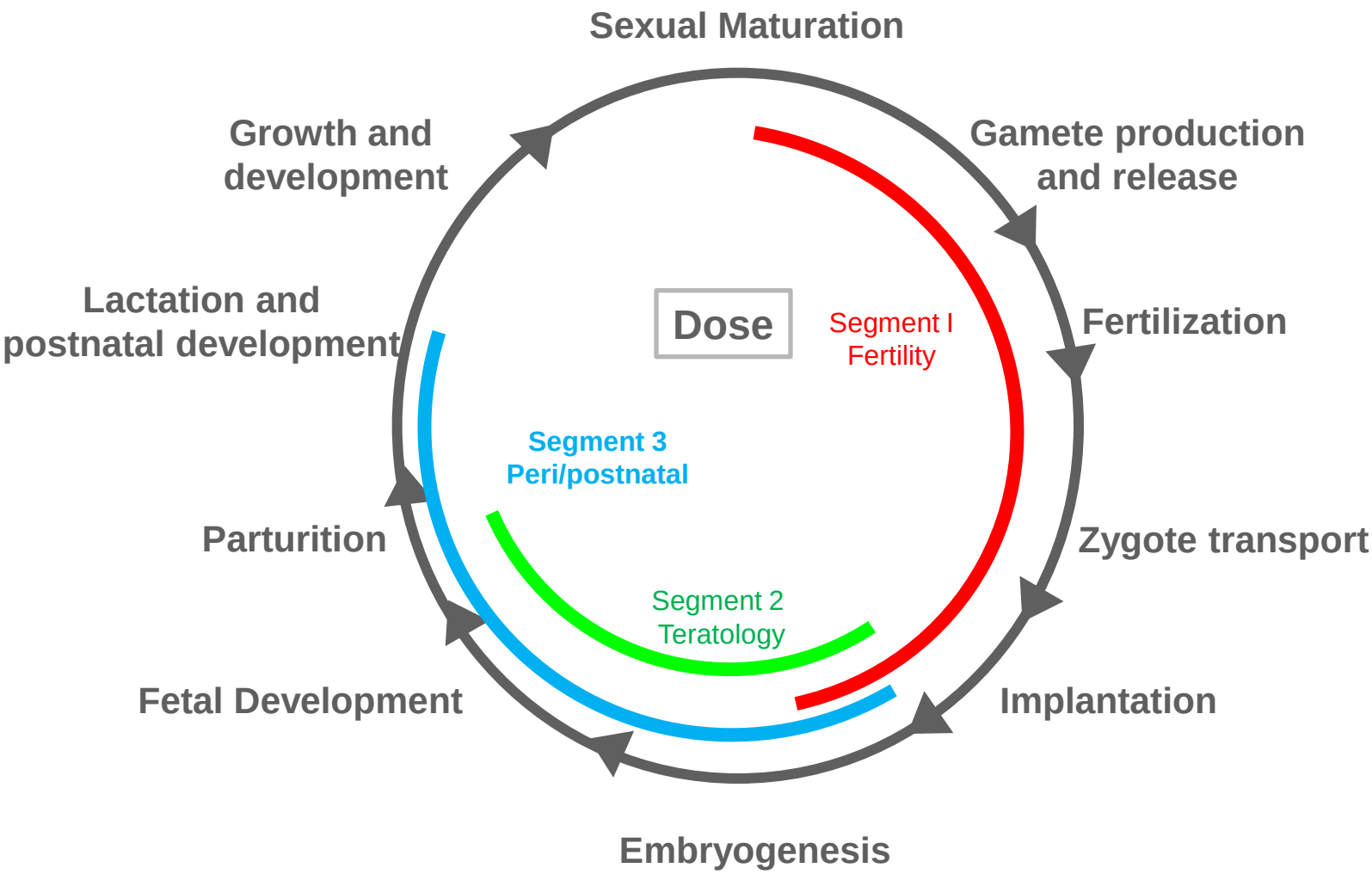
Unequivocally genotoxic compounds, in the absence of other data, are presumed to be trans-species carcinogens, implying a hazard to humans. Such compounds need not be subjected to long-term carcinogenicity studies. ***However, if such a drug is intended to be administered chronically to humans a chronic toxicity study (up to one year) may be necessary to detect early tumorigenic effects.***

- Longest duration of preclinical administration of hydroxyurea conducted by the Sponsor was three months (IP)
- Available carcinogenicity studies are inadequate?

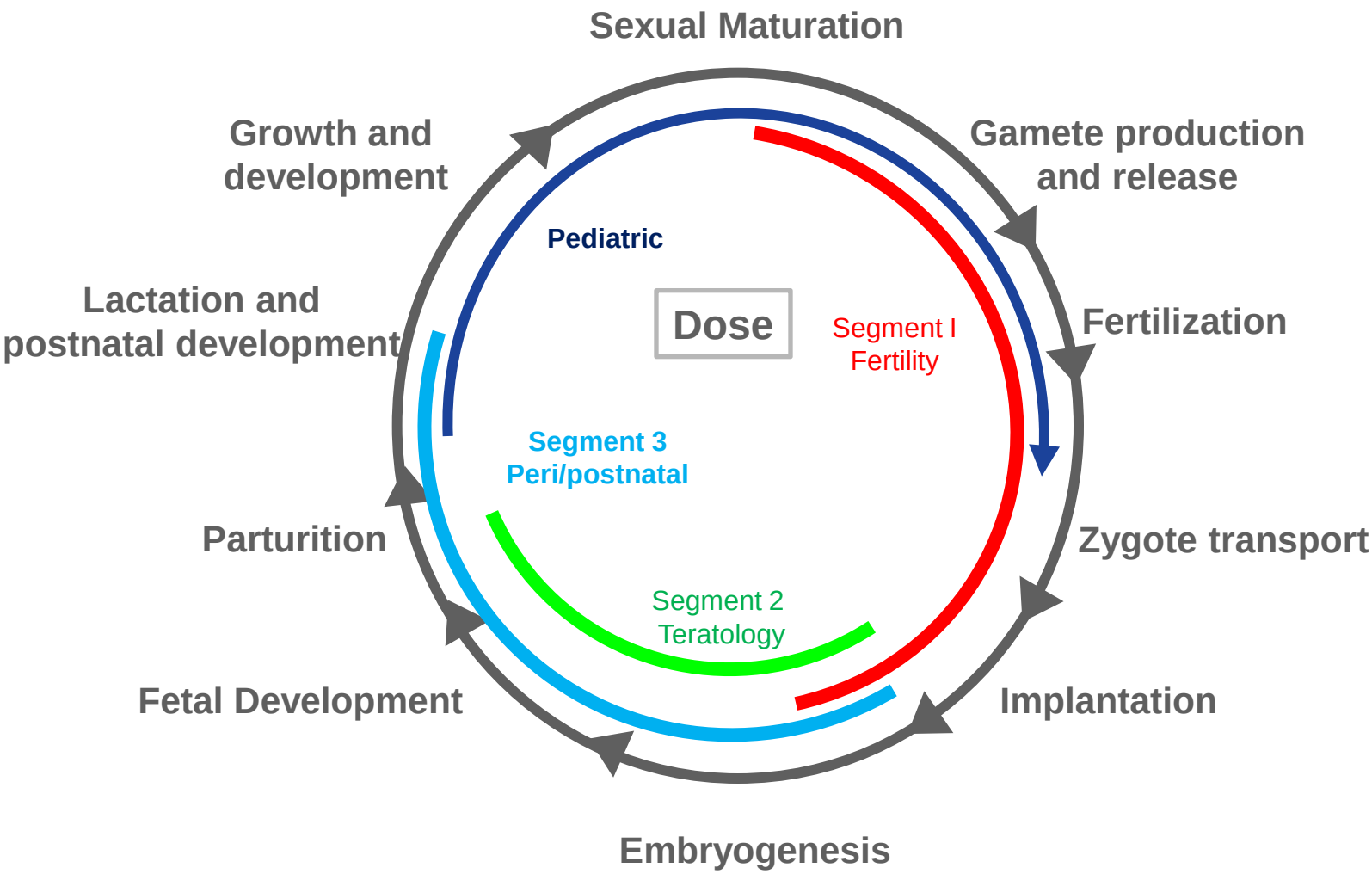
Hydroxyurea: Reproductive and Developmental Toxicity (NTP CERHR, 2007)

- Human Data
  - Few case reports of low sperm count; decreased sperm motility in human studies
  - Limited case reports on the use of hydroxyurea during pregnancy
    - Confounded by disease state
- Animal Data
  - Induces terata in multiple species, decreases in number of live births
  - Decreased testis weight and histologic abnormalities of seminiferous tubules in rats and mice; decreased sperm counts in mice; limited evidence of functional effects in rats (1990s)
    - Potential for reversibility unclear
  - Blood concentrations associated with some of these effects in animals similar to those in patients on therapy
  - Limited information suggests that hydroxyurea also affects neurological development and immune function

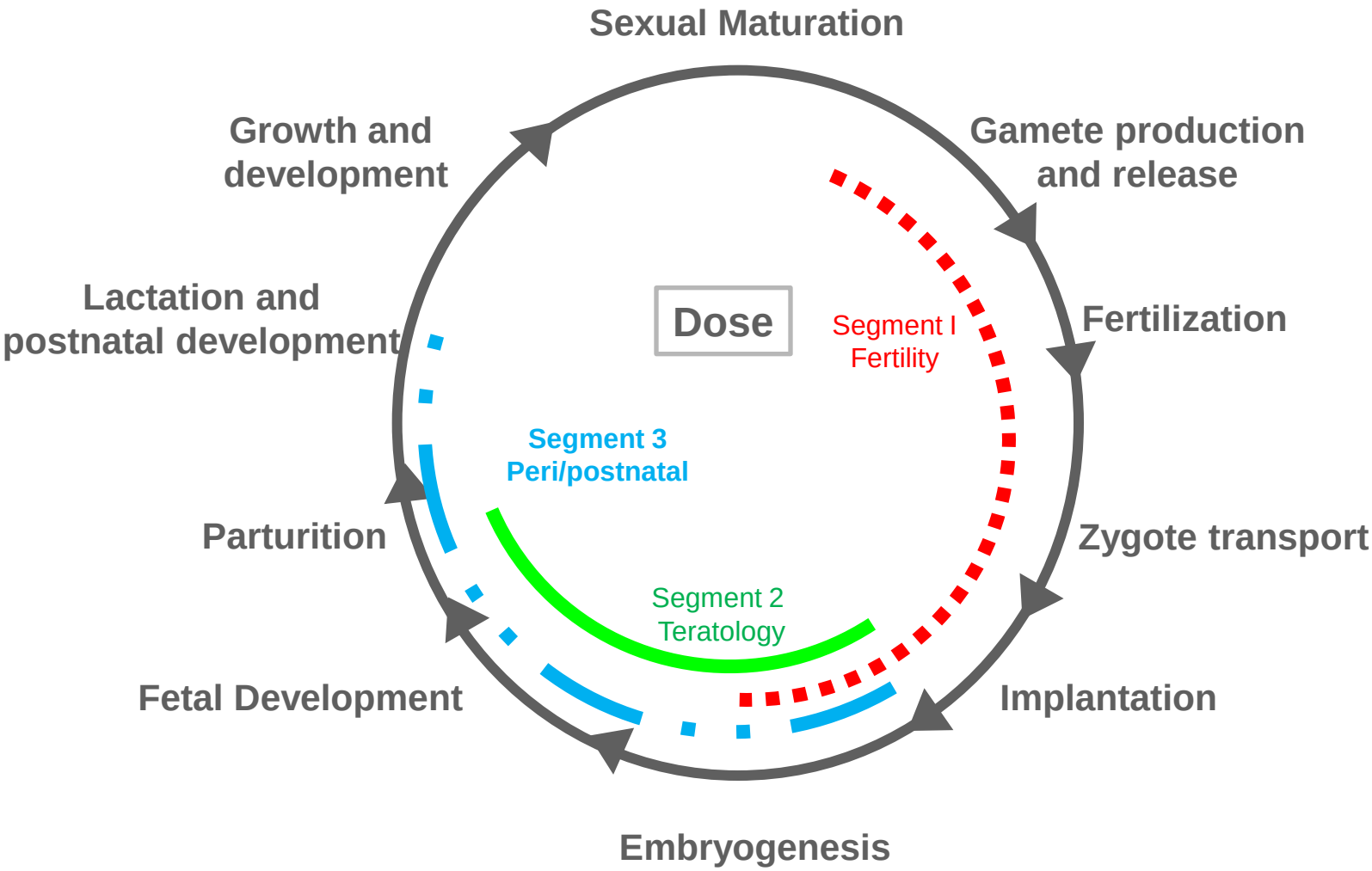
ICH S5R2 Segmented design



ICH S5R2 Segmented Design FDA/EMA Pediatric Design



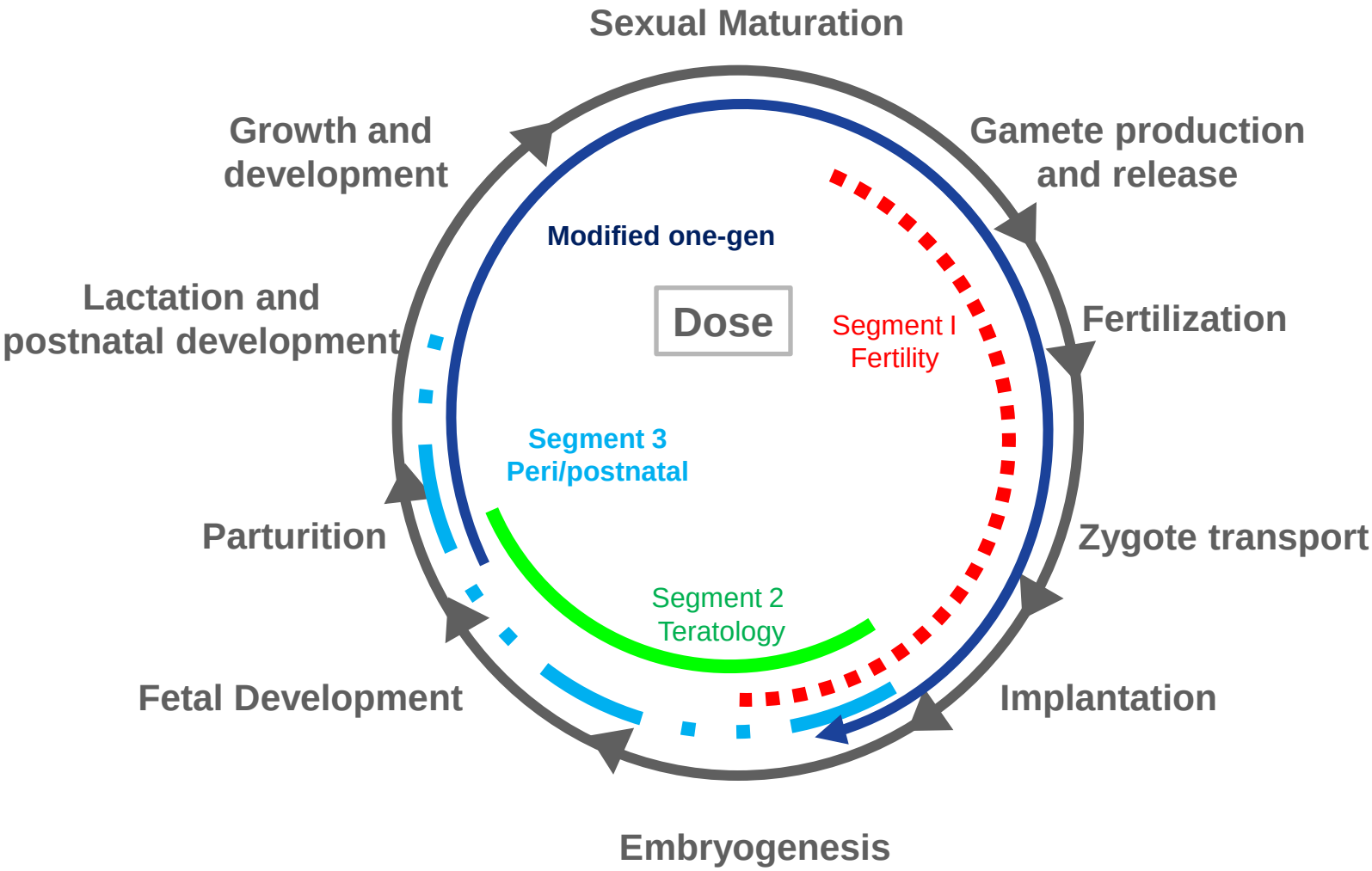
Hydroxyurea Reproductive and Developmental Toxicity Data "Robustness"



Hydroxyurea: Summary of Key Safety Issues

- Hydroxyurea is being used with increasing frequency in young children and infants (and pregnant women) for the treatment of sickle cell anemia and related diseases.
  - Very limited treatment options
- Hydroxyurea is also used in the treatment of some forms of cancers.
- There is limited information on the potential long-term consequences of hydroxyurea use in infants, children and adults.
- Potential effects on fertility, developmental outcomes, and carcinogenicity are lacking, particularly for chronic exposure beginning early in life.
- Data generated in rodents would provide important information to clinicians in counseling patients
  - Risks versus benefits of this therapy

Proposed Reproductive and Developmental Design will Cover



Specific Aims

- Generate toxicity information in rodents by dosing pregnant animals late in gestation, and directly dosing their offspring
- The offspring would be assessed for the following endpoints:
  - Fertility (including reversibility/recovery)
  - Neurobehavioral assessment/neurotoxicity
  - Immune function
  - Malformations, litter size, etc.
  - Carcinogenicity
  - Exposure/absorption, distribution, metabolism, and elimination (ADME)

Preliminary Study Plan

Tier 1

- Dose range-finding study followed by a full developmental toxicity modified one-generational design (peri-/post-natal administration)
  - Study will be consistent with FDA's *Guidance for Industry- Nonclinical Safety Evaluation of Pediatric Drug Products*
  - Pregnant rodents will be dosed late in gestation (dosing earlier will likely result in extensive terata/resorptions) and dose the subsequent offspring directly
    - Mimic the clinical dosing paradigm
  - The $F_0/F_1/F_2$ generation would be assessed for the following:
    - Effects on parturition, perinatal survival
    - Malformations, litter size, etc.
    - Fertility (including reversibility/recovery)
    - Neurobehavioral/toxicity assessment
    - Immune-function
    - Exposure (ADME)

Tier 2

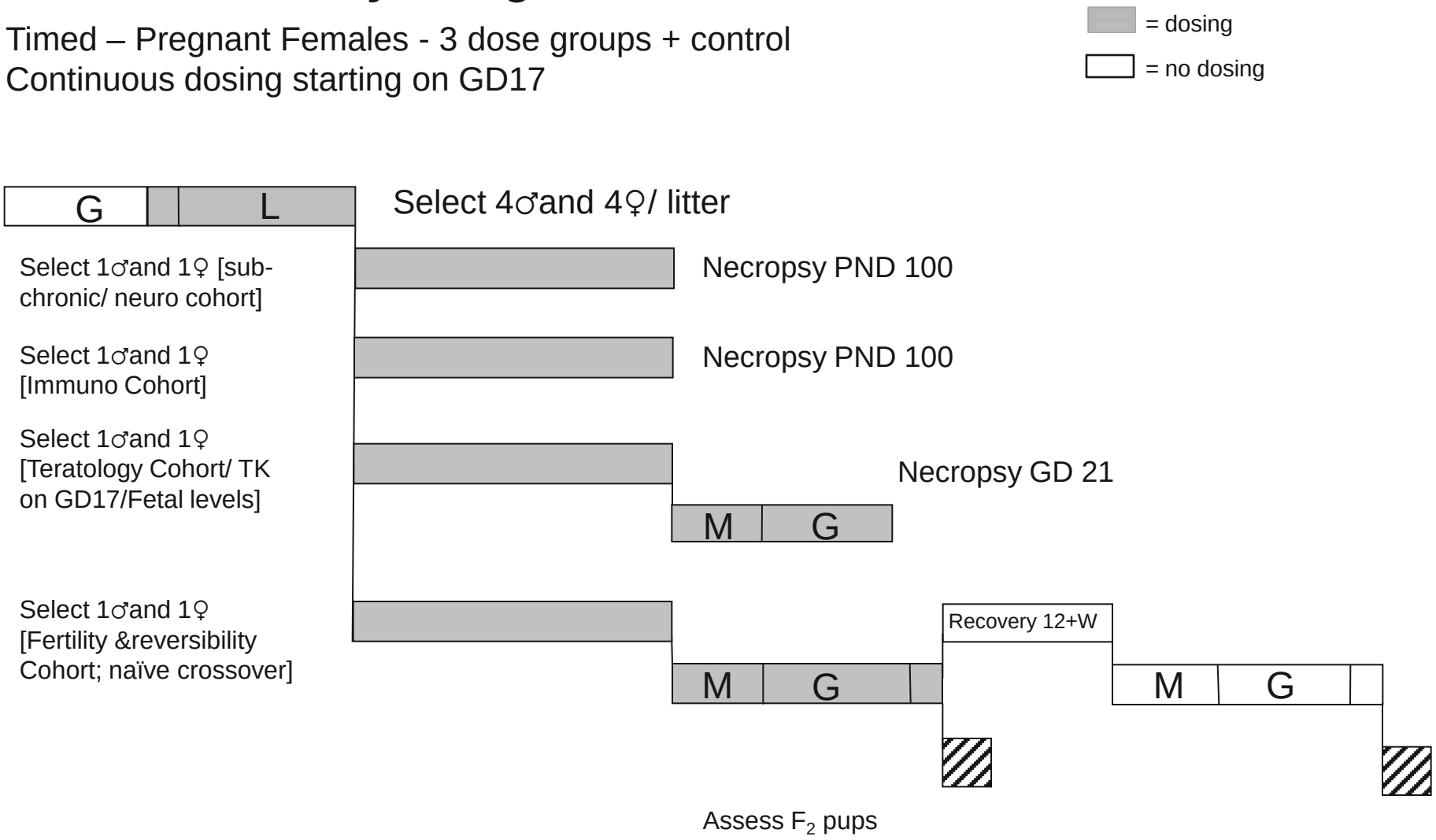
- Carcinogenicity assessments in rat and mouse

Significance and Expected Outcomes

- We hypothesize that toxic effects will be observed following exposure to hydroxyurea.
  - Prenatal and neonatal developmental periods will be particularly sensitive to the adverse effects of this drug.
- We further hypothesize that the immune, nervous, and reproductive systems will show developmental abnormalities and long term adverse effects.
  - Provide dose/response relationships as a function internal dose (relative to human exposure).
- Rat and mouse carcinogenic potential will be assessed.
- The expected data will provide critical information on long term outcomes to aid in risk-benefit decisions.
  - Provide health authorities (e.g., FDA and European Medicines Agency) information to assist in updating drug label information.
  - Better understanding of the risk/benefit may help spur research in developing a better therapy for sickle cell disease.

Potential Study Design

Timed – Pregnant Females - 3 dose groups + control
Continuous dosing starting on GD17



Overall CERHR Conclusions

The NTP expresses **serious concern** that exposure of men to therapeutic doses of hydroxyurea may adversely affect sperm production. This level of concern is for all males who have reached puberty.

The NTP concurs with the Expert Panel that there is **concern** that exposure of pregnant women to hydroxyurea may result in birth defects, abnormalities of fetal growth, or abnormal postnatal development in offspring.

The NTP concurs with the Expert Panel that there is **minimal concern** that exposure of children to therapeutic doses of hydroxyurea at 5 –15 years of age will adversely affect growth.